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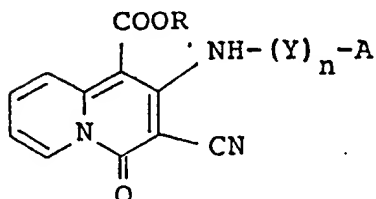
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⑤④ 4H-quinolizin-4-one compounds and pharmaceutical compositions containing them.

⑤⑦ The invention provides novel 4H-quinolizin-4-one compounds of the formula:



which exhibit a selective inhibitory activity against IgE-antibody formation, and have utility for treatment of diseases associated with IgE formation in mammals, such as allergic bronchial asthma, allergic rhinitis, atopic dermatitis and hypersensitivity. The invention also provides pharmaceutical compositions containing such compounds.

## Description

## 4H-QUINOLIZIN-4-ONE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to novel quinolizininone derivatives which are useful as therapeutic agents. More particularly, this invention provides 4H-quinolizinin-4-one compounds which exhibit selective inhibitory activities relative to IgE-antibody formation, and which have properties suitable for application as drugs for the treatment of diseases associated with IgE such as allergic bronchial asthma, allergic rhinitis, atopic dermatitis and hypersensitiveness.

Several classes of immunoglobulin(s) [hereinafter referred to as Ig(s)] are well known as antibodies concerned with immune response. Most of Igs, especially immunoglobulin G (hereinafter referred to as IgG) which is one class of Igs, play an important role in the self-defence mechanisms of mammals against foreign substances such as viruses, bacteria and tumours.

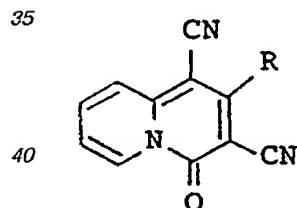
However, immunoglobulin E (hereinafter referred to as IgE) which is another class of Igs, has been confirmed to be primarily responsible for diseases such as allergic bronchial asthma, allergic rhinitis, atopic dermatitis and hypersensitiveness (Journal of Immunology, Vol. 10, p 445, 1925, Journal of Immunology, Vol. 97, p 75, 1966). It has also been confirmed that the serum concentrations of IgE in most allergic patients suffering from those diseases are generally higher than those in normal persons.

Therefore, selective inhibition of its formation might be an effective pharmacological approach for the treatment of allergy in humans. Attempts have been widely made to develop selective inhibitors of IgE formation. The prospective inhibitors preferably would not inhibit excessively any class of Igs except IgE for the reasons mentioned above.

Up to the present time, various compounds have been reported in the literature as inhibiting IgE formation such as Japanese Patent Application (OPI) No. 76/87 (the term "OPI" used herein refers to an unexamined Japanese patent application); U.S. Patent Nos. 4,395,405 and 4,691,018; British Patent Application No. 2,020,665(A) and J. Med. Chem. Vol. 25, No. 12, pages 1495-1499, 1982.

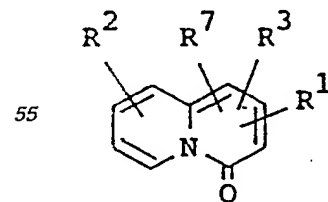
Of particular interest with respect to the present invention are publications which disclose compounds having a substituted 4H-quinolizinin-4-one nucleus.

Process for the production of 1-, 2- and 3- substituted 4H-quinolizinin-4-one derivatives are described in Yakugaku Zasshi, Vol. 89, No. 2, pages 203-208, 1969, *ibid.* Vol. 90, No. 2, pages 127-131, 1970, *ibid.* Vol. 91, No. 12, pages 1275-1278, 1971, *ibid.* Vol. 94, No. 1, pages 44-49, 1974, Chem. Pharm. Bull, Vol. 18, No. 1, pages 124-127, 1970, *ibid.* Vol. 21, No. 5, pages 921-925, 1973, J. Heterocycl. Chem., Vol. 10, No. 2, pages 139-142, 1973, J. Chem. Soc. (c), pages 1143-1146, 1969, Monatsh. Chem., Vol 114, pages 485-493, 1983. The anti-tumor activity of 1-, 2- and 3-substituted 4H-quinolizinin-4-one derivatives of the formula:



where R is methylthio, piperidino, N,N-diethyl aminoethylamino or benzylamino is disclosed in Yakugaku Zasshi, Vol 97, No. 9, pages 1039-1045, 1977.

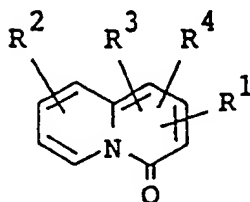
European Patent Application 157346(A<sub>2</sub>) and Japanese Patent Application (OPI) No. 222482/85 which are counterparts of British Patent Application Nos. 8408292 and 8429710, filed March 30, 1984 and November 23, 1984, respectively, disclose quinolizininone derivatives having an inhibitory activity on allergies and ulcers, which derivatives correspond to the formula:



where R<sup>1</sup> is carboxy, amidated carboxy, cyano, thiocarbamoyl or tetrazolyl; R<sup>7</sup> is hydrogen or aryl; R<sup>2</sup> is hydrogen, hydroxy, lower alkyl or lower alkoxy; R<sup>3</sup> is hydrogen, hydroxy, lower alkyl, lower alkoxy, lower alkenyloxy, aryl which may have suitable substituents, arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, arylamino

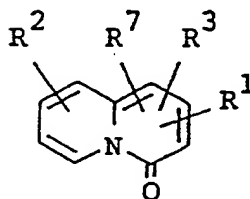
which may have a suitable substituent or aryloxy; and  $R^2$  and  $R^3$  can be located at any place on the quinolizine ring and can be linked together to form  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ ; and pharmaceutically acceptable salts thereof.

Japanese Patent Application (OPI) No. 77385/87 which is a counterpart of United States Patent Application Serial No. 770953 filed August 30, 1985, discloses quinolizininone derivatives having an inhibitory activity on allergies and ulcers, which derivatives correspond to the formula:



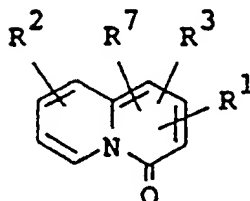
where  $R^1$  is carboxy, tetrazolylcarbamoyl or amino-substituted triazolylcarbamoyl;  $R^2$  is hydrogen or lower alkoxy;  $R^3$  is hydrogen, aroyl, aryl, carboxy or protected carboxy;  $R^4$  is hydrogen or hydroxy; with the proviso that (i) when  $R^3$  is hydrogen,  $R^4$  is hydroxy, ii) when  $R^3$  is aryl,  $R^1$  is amino-substituted triazolylcarbamoyl and (iii) when  $R^3$  is aroyl,  $R^2$  is lower alkoxy; and pharmaceutically acceptable salts thereof.

United States Patent No. 4,650,804 which is a counterpart of British Patent Application Nos. 8408292 and 8429710, filed March 30, 1984 and November 23, 1984, respectively, disclose quinolizininone derivatives having an inhibitory activity on allergies and ulcers, which derivatives correspond to the formula:



where  $R^1$  is tetrazolylcarbamoyl;  $R^7$  is hydrogen or aryl selected from phenyl, tolyl, xylyl, cumenyl, naphthyl and biphenyl;  $R^2$  is hydrogen, hydroxy, lower alkyl or lower alkoxy;  $R^3$  is hydrogen, hydroxy, lower alkyl, lower alkoxy, lower alkenyloxy, phenyl, naphthyl, biphenyl, phenyl having one or more substituents selected from halogen, lower alkyl and lower alkoxy, arylthio selected from phenylthio, tolylthio, xylylthio, cumenylthio, naphthylthio and biphenylthio, aroyl selected from benzoyl, toluoyl and naphthoyl, ar(lower)alkyl selected from phenyl(lower)alkyl, tolyl(lower)alkyl, xylyl(lower)alkyl, cumenyl(lower)alkyl, naphthyl(lower)alkyl and biphenyl(lower)alkyl, arenesulfonyl selected from benzenesulfonyl and p-toluenesulfonyl, arylamino selected from phenylamino, naphthylamino, biphenylamino, phenylamino having lower alkyl on the nitrogen atom or aryloxy selected from phenoxy and tolyloxy; or pharmaceutically acceptable salts thereof.

United States Patent No. 4,698,349 filed August 30, 1985, disclose quinolizininone derivatives having an inhibitory activity on allergies and ulcers, which derivatives correspond to the formula:



where  $R^1$  is carboxy, carbamoyl, phenylcarbamoyl which may have hydroxy, cyano or thiocarbamoyl;  $R^7$  is hydrogen or aryl selected from phenyl, tolyl, xylyl, cumenyl, naphthyl and biphenyl;  $R^2$  is hydrogen, hydroxy, lower alkyl or lower alkoxy;  $R^3$  is hydrogen, hydroxy, lower alkyl, lower alkoxy, lower alkenyloxy, phenyl, naphthyl, biphenyl, phenyl having one or more substituents selected from halogen, lower alkyl and lower

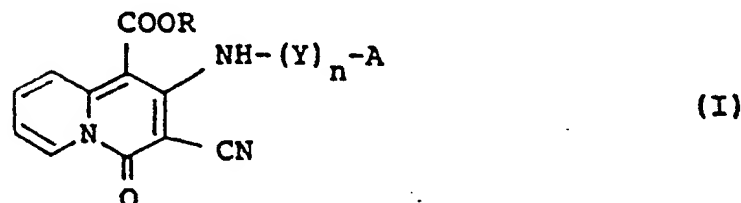
alkoxy, arylthio selected from phenylthio, tolylthio, xylylthio, cumenylthio, naphthylthio and biphenylthio, aroyl selected from benzoyl, toluoyl and naphthoyl, ar(lower)alkyl selected from phenyl(lower)alkyl, tolyl(lower)alkyl, xylyl(lower)alkyl, cumenyl(lower)alkyl, naphthyl(lower)alkyl and biphenyl(lower)alkyl, arenesulfonyl selected from benzenesulfonyl and p-toluenesulfonyl, arylamino selected from phenylamino, naphthylamino, biphenylamino, phenylamino having lower alkyl on the nitrogen atom or aryloxy selected from phenoxy and tolyloxy; or pharmaceutically acceptable salts thereof.

In none of the publications described above is there any disclosure or suggestion that novel substituted 4H-quinolizin-4-one of the type provided by the present invention might exhibit an inhibitory activity against IgE formation in mammals.

As an invention related to the present invention, the present inventors have filed U.S. Patent Application S.N. 147,549, on January 25, 1988.

The present invention provides novel quinolizone derivatives which exhibit selective inhibitory activities against IgE formation when administered to humans or to other mammals, and pharmaceutical compositions comprising these quinolizone derivatives.

The present invention provides novel 4H-quinolizin-4-one derivatives of the general formula:



where R is an alkyl group or a phenylalkyl group; Y is an alkylene group; n is zero or 1; A is a substituted or unsubstituted 5 or 6 membered aromatic heterocyclic ring, a substituted or unsubstituted 3 to 7 membered cycloalkyl group or a substituted or unsubstituted 5 to 7 membered saturated heterocyclic ring, and pharmaceutically acceptable salts thereof.

In the above and subsequent description of the present specification, the terms used in the definitions of the symbols have the following meanings.

The term "alkyl" and the "alkyl" moiety in "phenylalkyl" refer to a straight or branched alkyl group having 1 to 6 carbon atoms.

The term "alkoxy" refers to a straight or branched alkoxy group having 1 to 6 carbon atoms.

The term "alkylene" refers to a straight or branched alkylene group having 1 to 6 carbon atoms.

The term "a 5 or 6 membered aromatic heterocyclic ring" refers to a 5 or 6 membered aromatic heterocyclic ring which contains one or more hetero atoms, such as pyrrole, furan, thiophen, imidazole, triazole, oxazole, oxadiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine and pyrazine.

The substituent or substituents which may be attached to the 5 or 6 membered aromatic heterocyclic ring defined above are selected from an alkyl group, amino group and nitro group.

The term "a 3 to 7 membered cycloalkyl group" refers to a saturated or unsaturated 3 to 7 membered cycloalkyl group which may be condensed with a hydrocarbon ring.

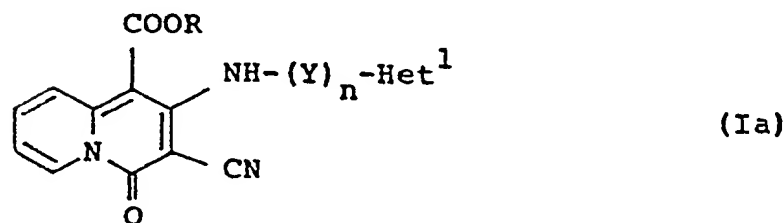
The substituent or substituents which may be attached to the 3 to 7 membered cycloalkyl group are selected from an alkyl group and an alkoxy group.

The term "a 5 to 7 membered saturated heterocyclic ring" refers to a 5 to 7 membered saturated heterocyclic ring containing one or more hetero atoms which may be the same or different.

When the 5 to 7 membered saturated heterocyclic ring defined above contains a nitrogen atom in the ring, the ring can be connected to the quinolizone ring through the -NH-(Y)<sub>n</sub>- chain at a carbon atom or the nitrogen atom in the ring.

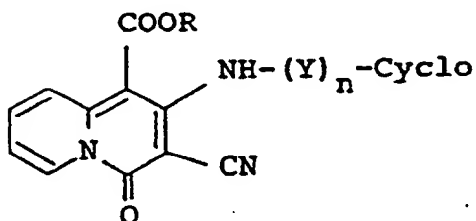
The substituent or substituents which may be attached to the 5 to 7 membered saturated heterocyclic ring are selected from an alkyl group and an alkoxy group.

In a preferred embodiment this invention provides a 4H-quinolizin-4-one compound of the formula:



where R, Y and n are as previously defined; Het<sup>1</sup> is a substituted or unsubstituted 5 or 6 membered aromatic heterocyclic group.

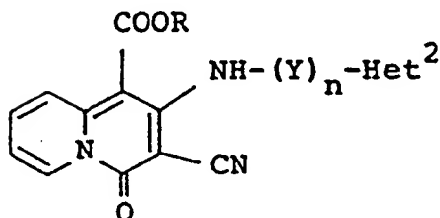
In another preferred embodiment this invention provides a 4H-quinolizin-4-one compound of the formula:



(Ib)

where R, Y and n are as previously defined; Cyclo is a substituted or unsubstituted 3 to 7 membered cycloalkyl group.

In another preferred embodiment this invention provides a 4H-quinolizin-4-one compound of the formula:



(Ic)

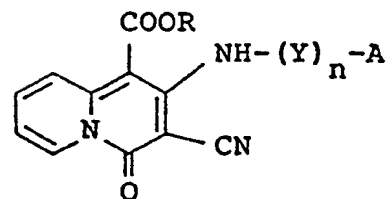
where R, Y and n are as previously defined; Het<sup>2</sup> is a substituted or unsubstituted 5 to 7 membered saturated heterocyclic group.

The 4H-quinolizin-4-one derivatives of the present invention selectively inhibit the formation of IgE.

Pharmacological test data indicates that the 4H-quinolizin-4-one derivatives of formula (I) of the present invention have potential utility as drugs for diseases associated with IgE, such as allergic bronchial asthma, allergic rhinitis, atopic dermatitis and hypersensitiveness.

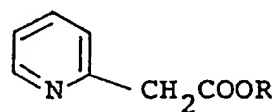
The 4H-quinolizin-4-one compounds of formula (I) of the present invention may be prepared according to the method described by Kobayashi et al. in Yakugaku Zasshi Vol. 89, No. 2, pp 203-208, 1969.

That is, a 4H-quinolizin-4-one derivative of the present invention corresponding to the formula:



(I)

where R, Y, n and A are as previously defined, can be prepared by the reaction of a compound corresponding to the formula:

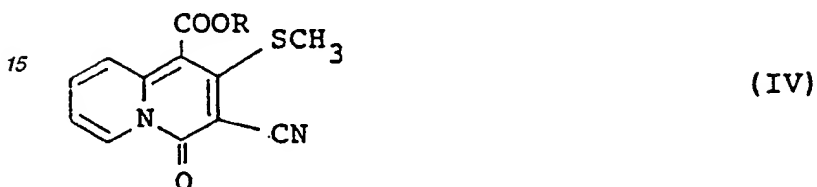


(II)

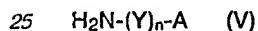
where R is as previously defined, with a compound corresponding to the formula:



10 to prepare a compound corresponding to the formula:



where R is as previously defined, followed by the reaction of the compound of formula (IV) above obtained with an amino compound corresponding to the formula:



where A, n and Y are as previously defined.

Compounds of formulae (II) and (III) for use as starting materials can be prepared as follows:

30 A compound of formula (II) can be prepared from 2-pyridylacetic acid according to the manner described in Compendium of Organic Synthetic Methods, Ed. by I.T. Harrison and S. Harrison, Wiley-Interscience New York, Vol. 1, pp 272-279, 1971.

A compound of formula (III) can be prepared by the reaction of methyl cyanoacetate, carbon disulfide and a dimethyl sulfate in accordance with a procedure described in Chemische Berichte, Vol. 95, pp 2861-2870, 1962.

35 The reaction of a compound of formula (II) with a compound of formula (III) can be conducted in accordance with the following preferred method.

A mixture of a compound of formula (II) and a compound of formula (III) in equal molar quantities is heated at 100-120°C for 2-10 hours, in the presence or absence of organic solvent, and then the reaction mixture is worked up to conventional procedures to obtain a compound of formula (IV).

40 And then the compound of formula (IV) above obtained is reacted with a compound of formula (V) in equal molar or excess quantities at a temperature from room temperature to 140°C for 2-48 hours, in the presence or absence of organic solvent, and the reaction mixture is worked up to conventional procedures to obtain the 4H-quinolizin-4-one compound of formula (I).

45 The 4H-quinolizin-4-one derivatives represented by formula (I) of the present invention exhibit selective inhibitory activities on IgE formation. The inhibitory activities of the quinolizinone derivatives of formula (I) are confirmed by the determination of IgS produced in cultures of spleen cells from BALB/c mice which exhibit an adoptive secondary immune response against dinitrophenylated proteins of ascaris (DNP-As) according to a procedure described in Cellular Immunology, Vol. 58, pp 188-201, 1981. And the inhibitory activities of the quinolizinone derivative of formula (I) are further confirmed by the determination of serum concentrations of IgS in BALB/c mice which are immunized by DNP-As according to a procedure described in Immunology, Vol 50 21, pp 11-12, 1971.

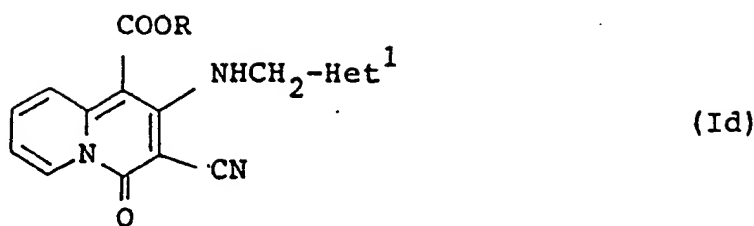
The results obtained by these tests demonstrate that the compounds of formula (I) of the present invention inhibit IgE formation, and minimally affect the production of IgS other than IgE.

55 From the results obtained by these pharmacological tests, it can be expected that the compound of formula (I) of the present invention has properties suitable for application as a therapeutic agent for treatment of diseases associated with IgE in mammals.

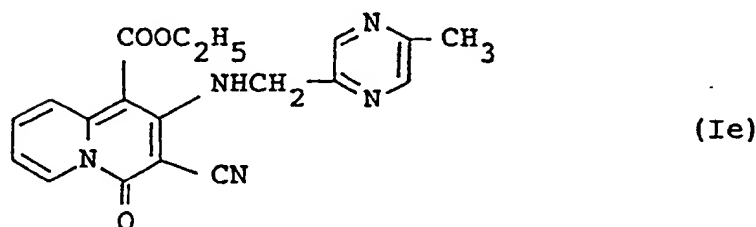
Furthermore, the compounds of the formula (I) of the present invention also selectively inhibit IgE production in cultures of peripheral blood lymphocytes from atopic patients.

60 An acute toxicological test in mice shows that the compounds of formula (I) of the present invention have very low acute toxicity.

Of the 4H-quinolizin-4-one compounds represented by the formula (I), the compounds represented by the formula:



where R and Het<sup>1</sup> are as previously defined are preferable, and the compounds wherein Het<sup>1</sup> is pyrazinyl having an alkyl group on the ring as a substituent are more preferable. The most preferred compound is 3-cyano-1-ethoxycarbonyl-2-(5-methylpyrazinyl)methylamino-4H-quinolizin-4-one represented by the formula:



The 4H-quinolizin-4-one derivatives of the general formula (I) of the present invention can be administered in various dosage forms depending upon the intended therapy. Typical dosage forms which can be used are tablets, pills, powder, liquid preparations, suspensions, emulsions, granules, capsules, suppositories, and injectable preparations.

In molding the pharmaceutical compositions into a tablet form, a wide variety of conventional carriers known in the art can be used. Examples of suitable carriers are excipients such as glucose, lactose, starch, cacao butter, hardened vegetable oils, kaolin and talc; binders such as gum arabic powder, tragacanth powder, and ethanol; and disintegrants such as laminaria and agar. The tablets, if desired, can be coated and made into sugar-coated tablets, gelatin-coated tablets, film-coated tablets, or tablets coated with two or more layers.

When a pharmaceutical composition is formulated into an injectable preparation, it is preferred that the resulting injectable solution and suspension are sterilized and rendered isotonic with respect to blood. In making the pharmaceutical composition into a solution or suspension, any diluents customarily used in the art can be employed. Examples of suitable diluents include water, ethyl alcohol, propylene glycol, polyoxyethylene sorbitol, and sorbitan esters. Sodium chloride, glucose or glycerol may be incorporated into a therapeutic agent in an amount sufficient to prepare an isotonic solution. The therapeutic agent may further contain ordinary dissolving aids, buffers, pain-alleviating agents, and preservatives, and optionally, coloring agents, fragrances, flavors, sweeteners, and other pharmacologically active agents.

The dosage of the quinolizone derivatives of the present invention may be in a range from approximately 0.1 mg to 10 mg per kg by an oral administration, or from about 0.02 mg to 5 mg per kg by a parenteral administration per day in multiple doses depending upon the type of disease, the severity of condition to be treated, and the like.

In another embodiment this invention provides a method for the treatment of diseases associated with IgE in a mammal which comprises administering an effective dosage of an IgE-formation-inhibiting 4H-quinolizin-4-one compound to the mammal.

In a further embodiment this invention provides a pharmaceutical composition for the treatment of diseases associated with IgE in a mammal, which composition contains an effective dosage of an IgE-formation-inhibiting 4H-quinolizin-4-one compound.

This invention is further illustrated in more detail by way of the following examples and pharmacological data.

#### Example 1

##### 3-Cyano-1-ethoxycarbonyl-2-(2-pyridylmethylamino)-4H-quinolizin-4-one (S-1)

A mixture of 1.53 g of 3-cyano-1-ethoxycarbonyl-2-methylthio-4H-quinolizin-4-one and 4.93 g of 2-aminomethylpyridine was stirred for 17 hours at room temperature. The precipitated crystals were collected by filtration and recrystallized from methanol to give 1.68 g of 3-cyano-1-ethoxycarbonyl-2-(2-pyridylmethyl-

lamino)-4H-quinolizin-4-one.

Melting point: 176.5-177°C

IR (KBr): 2200, 1695, 1655, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

5 δ 1.46(t, 3H), 4.51(q, 2H), 5.22(d, 2H), 6.92(t, 1H), 7.27(t, 1H), 7.34(d, 1H), 7.51(dt, 1H), 7.72(dt, 1H), 8.25(d, 1H), 8.62(d, 1H), 9.06(d, 1H), 9.62(br, 1H)

Elementary analysis: C<sub>19</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>

	C%	H%	N%
10 Calcd.	65.51	4.63	16.08
Found	65.44	4.68	15.69

## 15 Example 2

The following compounds were obtained according to the same procedure as described in Example 1.

## 3-Cyano-1-ethoxycarbonyl-2-[2-(2-pyridyl)ethylamino]-4H-quinolizin-4-one (S-2)

Melting point: 123-124°C

20 IR (KBr): 2200, 1670, 1625 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.40(t, 3H), 3.25(t, 2H), 4.28(q, 2H), 4.41(q, 2H), 6.90(t, 1H), 7.19(dt, 1H), 7.31(d, 1H), 7.50(dt, 1H), 7.68(dt, 1H), 8.17(d, 1H), 8.57(d, 1H), 8.85(br, 1H), 9.06(d, 1H)

Elementary analysis: C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>

	C%	H%	N%
25 Calcd.	66.29	5.01	15.46
Found	66.19	5.02	15.43

30

## 3-Cyano-1-(3-phenylpropoxycarbonyl)-2-[2-(2-pyridyl)ethylamino]-4H-quinolizin-4-one (S-3)

amorphous solid

IR (KBr): 2200, 1650, 1620 cm<sup>-1</sup>35 <sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 2.08(m, 2H), 2.73(t, 2H), 3.25(t, 2H), 4.29(q, 2H), 4.37(t, 2H), 6.91(dt, 1H), 7.12-7.33(m, 7H), 7.49(dt, 1H), 7.65(dt, 1H), 8.13(d, 1H), 8.52(d, 1H), 8.87(br, 1H), 9.06(d, 1H)

Elementary analysis: C<sub>27</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>

	C%	H%	N%
40 Calcd.	71.67	5.35	12.38
Found	71.89	5.42	12.64

45

## 3-Cyano-1-ethoxycarbonyl-2-(2-furylmethylamino)-4H-quinolizin-4-one (S-4)

Melting point: 142-143°C

IR (KBr): 2200, 1670, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

50 δ 1.39(t, 3H), 4.42(q, 2H), 5.06(d, 2H), 6.39(m, 1H), 6.43(m, 1H), 6.98(t, 1H), 7.43(m, 1H), 7.57(dt, 1H), 8.31(d, 1H), 9.00(br, 1H), 9.12(d, 1H)

Elementary analysis: C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>

	C%	H%	N%
55 Calcd.	64.09	4.48	12.46
Found	63.88	4.48	12.32

## 60 3-Cyano-2-(2-furylmethylamino)-1-(3-phenylpropoxycarbonyl)-4H-quinolizin-4-one (S-5)

Melting point: 150-151°C

IR (KBr): 2210, 1680, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

65 δ 2.08(m, 2H), 2.75(t, 2H), 4.37(t, 2H), 5.07(d, 2H), 6.36(m, 1H), 6.42(m, 1H), 6.99(t, 1H), 7.15-7.33(m, 5H), 7.39(m, 1H), 7.56(dt, 1H), 8.29(d, 1H), 9.03(br, 1H), 9.11(d, 1H)



	C%	H%	N%
Calcd.	61.89	4.33	20.05
Found	61.84	4.21	19.68

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3-Cyano-1-ethoxycarbonyl-2-(3-methylpyrazinyl)methylamino-4H-quinolizin-4-one (S-15)

Melting point: 198-200°C

IR (KBr): 2200, 1690, 1670, 1620 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.50(t, 3H), 2.66(brs, 3H), 4.55(q, 2H), 5.25(d, 2H), 6.96(t, 1H), 7.54(dt, 1H), 8.29(d, 1H), 8.46(d, 1H), 8.48(d, 1H), 9.09(d, 1H), 9.79(br, 1H)

Elementary analysis: C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>

10

	C%	H%	N%
Calcd.	62.80	4.72	19.27
Found	63.01	4.68	19.46

15

3-Cyano-1-ethoxycarbonyl-2-(5-methylpyrazinyl)methylamino-4H-quinolizin-4-one (S-16)

Melting point: 183-186°C

IR (KBr): 2200, 1690, 1650, 1625 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.47(t, 3H), 2.60(brs, 3H), 4.49(q, 2H), 5.25(d, 2H), 6.97(t, 1H), 7.58(dt, 1H), 8.29(d, 1H), 8.50(brs, 1H), 8.59(brs, 1H), 9.10(d, 1H), 9.55(br, 1H)

Elementary analysis: C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>

20

25

	C%	H%	N%
Calcd.	62.80	4.72	19.27
Found	62.91	4.69	19.44

30

3-Cyano-1-ethoxycarbonyl-2-(6-methylpyrazinyl)methylamino-4H-quinolizin-4-one (S-17)

Melting point: 167-168°C

IR (KBr): 2210, 1670, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.46(t, 3H), 2.63(brs, 3H), 4.49(q, 2H), 5.25(d, 2H), 6.96(t, 1H), 7.56(dt, 1H), 8.27(d, 1H), 8.45(brs, 1H), 8.49(brs, 1H), 9.10(d, 1H), 9.52(br, 1H)

Elementary analysis: C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>

35

40

	C%	H%	N%
Calcd.	62.80	4.72	19.27
Found	62.40	4.06	19.07

45

3-Cyano-1-ethoxycarbonyl-2-[2-(5-nitropyridin-2-ylamino)ethylamino]-4H-quinolizin-4-one (S-18)

Melting point: 197-199°C

IR (KBr): 2200, 1650, 1630, 1540, 1330 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.28(t, 3H), 3.84(m, 2H), 3.94(m, 2H), 4.28(q, 2H), 6.58(d, 1H), 7.14(t, 1H), 7.76(dt, 1H), 8.03-8.34(m, 4H), 8.87-8.95(m, 2H)

Elementary analysis: C<sub>20</sub>H<sub>18</sub>N<sub>6</sub>O<sub>5</sub>

50

55

	C%	H%	N%
Calcd.	56.87	4.30	19.90
Found	56.42	4.42	19.77

60

3-Cyano-1-ethoxycarbonyl-2-[2-(1-methylpyrrol-2-yl)ethylamino]-4H-quinolizin-4-one (S-19)

Melting point: 145-147°C

IR (KBr): 2200, 1675, 1630 cm<sup>-1</sup>

65

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.38(t, 3H), 3.00(t, 2H), 3.60(s, 3H), 4.13(q, 2H), 4.39(q, 2H), 6.06(m, 2H), 6.59(m, 1H), 6.92(t, 1H), 7.53(dt, 1H), 8.21(d, 1H), 8.85(br, 1H), 9.08(d, 1H)

Elementary analysis: C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>

5

	C%	H%	N%
Calcd.	65.92	5.53	15.37
Found	65.90	5.48	15.64

10

3-Cyano-1-ethoxycarbonyl-2-imidazolylmethylamino-4H-quinolizin-4-one (S-20)

Melting point: 239°C (decomp.)

IR (KBr): 2220, 1680, 1640, 1620 cm<sup>-1</sup>

15

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.43(t, 3H), 4.48(q, 2H), 5.18(d, 2H), 6.98(t, 1H), 7.11(brs, 2H), 7.30(br, 1H), 7.57(dt, 1H), 8.29(d, 1H), 9.07(d, 1H), 9.40(br, 1H)

Elementary analysis: C<sub>17</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>

20

	C%	H%	N%
Calcd.	60.53	4.48	20.76
Found	60.62	4.41	20.88

25

3-Cyano-1-ethoxycarbonyl-2-(4-imidazolylmethylamino)-4H-quinolizin-4-one (S-21)

Melting point: 245-248°C (decomp.)

IR (KBr): 2200, 1670, 1635 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

30

δ 1.29(t, 3H), 4.35(q, 2H), 4.83(d, 2H), 7.16(m, 2H), 7.69(brs, 1H), 7.79(dt, 1H), 8.18(d, 1H), 8.63(br, 1H), 8.94(d, 1H), 12.10(br, 1H)

Elementary analysis: C<sub>17</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>

35

	C%	H%	N%
Calcd.	60.53	4.48	20.76
Found	60.01	4.57	20.59

40

## Example 3

3-Cyano-1-methoxycarbonyl-2-(2-pyridylmethylamino)-4H-quinolizin-4-one (S-22)

To a solution of 3.00 g of 3-cyano-1-ethoxycarbonyl-2-(2-pyridylmethylamino)-4H-quinolizin-4-one in 1000 ml of abs. methanol was added 40 mg of sodium hydride and the reaction mixture was heated under reflux for 3 hours. After cooling, the precipitated crystals were collected by filtration to give 2.56 g of 3-cyano-1-methoxycarbonyl-2-(2-pyridylmethylamino)-4H-quinolizin-4-one.

45

Melting point: 231°C (decomp.)

IR (KBr): 2200, 1690, 1650, 1620 cm<sup>-1</sup><sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):

50

δ 4.03(s, 3H), 5.37(d, 2H), 7.33(t, 1H), 7.85-7.96(m, 3H), 8.24(d, 1H), 8.44(d, 1H), 8.87-8.97(m, 2H), 9.05(d, 1H)

Elementary analysis: C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>

55

	C%	H%	N%
Calcd.	64.67	4.22	16.76
Found	64.74	4.21	16.53

60

## Example 4

3-Cyano-1-methoxycarbonyl-2-(2-pyridylmethylamino)-4H-quinolizin-4-one hydrochloride (S-23)

3-Cyano-1-methoxycarbonyl-2-(2-pyridylmethylamino)-4H-quinolizin-4-one (1.00 g) was dissolved in 3 ml of concentrated hydrochloric acid and the excess hydrochloric acid was evaporated under reduced pressure. Diethyl ether (50 ml) was added to the residue and the precipitated crystals were collected by filtration to give 1.01 g of 3-cyano-1-methoxycarbonyl-2-(2-pyridylmethylamino)-4H-quinolizin-4-one hydrochloride.

65

Melting point: 220°C (decomp.)

IR (KBr): 2200, 1680, 1645, 1615 cm<sup>-1</sup>

<sup>1</sup>H-NMR DMSO-d<sub>6</sub>:

δ 4.04(s, 3H), 5.28(d, 2H), 7.31(t, 1H), 7.69-7.80(m, 3H), 7.95(dt, 1H), 8.20-8.30(m, 2H), 8.86(d, 1H), 9.05(d, 2H)

Elementary analysis: C<sub>18</sub>N<sub>15</sub>N<sub>45</sub>O<sub>3</sub>Cl

5

	C%	H%	N%
Calcd.	58.31	4.08	15.51
Found	58.35	4.04	15.59

10

#### Example 5

##### 3-Cyano-2-cyclohexylamino-1-ethoxycarbonyl-4H-quinolizin-4-one (S-24)

15

To a solution of 288 mg of 3-cyano-1-ethoxycarbonyl-2-methylthio-4H-quinolizin-4-one in acetonitrile, was added 1.14 ml of cyclohexylamine and the reaction mixture was stirred for 4 hours at room temperature. The solvent was evaporated and the residue was triturated with methanol. The crude crystals were recrystallized from dichloromethane-methanol to give 210 mg of 3-cyano-2-cyclohexylamino-1-ethoxycarbonyl-4H-quinolizin-4-one.

20

Melting point: 140-141°C

IR (KBr): 2200, 1675, 1630 cm<sup>-1</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.20-1.83(m, 11H), 2.16(br, 2H), 4.44(q, 2H), 4.50(m, 1H), 6.90(t, 1H), 7.51(dt, 1H), 8.21(d, 1H), 8.89(br, 1H), 9.08(d, 1H)

25

Elementary analysis: C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>

	C%	H%	N%
Calcd.	67.24	6.24	12.38
Found	67.27	6.40	12.65

30

#### Example 6

The following compounds were obtained according to the same procedure as described in Example 5.

35

##### 3-Cyano-1-ethoxycarbonyl-2-[2-(1-pyrrolidinyl)ethylamino]-4H-quinolizin-4-one (S-25)

Melting point: 74-75°C

IR (KBr): 2220, 1650, 1620 cm<sup>-1</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.43(t, 3H), 1.88(br, 4H), 2.65(br, 4H), 2.85(br, 2H), 4.03(br, 2H), 4.45(q, 2H), 6.92(t, 1H), 7.51(t, 1H), 8.21(d, 1H), 8.69(br, 1H), 9.06(d, 1H)

40

Elementary analysis: C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>

	C%	H%	N%
Calcd.	64.39	6.26	15.81
Found	64.68	6.36	15.89

45

##### 3-Cyano-1-(3-phenylpropoxycarbonyl)-2-[2-(1-pyrrolidinyl)ethylamino]-4H-quinolizin-4-one (S-26)

50

Melting point: 75-76°C

IR (KBr): 2220, 1650, 1625 cm<sup>-1</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.81(br, 4H), 2.12(m, 2H), 2.62(br, 4H), 2.76(t, 2H), 2.83(br, 2H), 3.99(br, 2H), 4.39(t, 2H), 6.90(t, 1H), 7.16-7.34(m, 5H), 7.50(dt, 1H), 8.18(d, 1H), 8.72(br, 1H), 9.06(d, 1H)

55

Elementary analysis: C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>

	C%	H%	N%
Calcd.	70.25	6.35	12.60
Found	70.21	6.47	12.79

60

##### 3-Cyano-2-cyclopropylmethylamino-1-ethoxycarbonyl-4H-quinolizin-4-one (S-27)

65

Melting point: 109-111°C

IR (KBr): 2205, 1165, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 0.38(m, 2H), 0.67(m, 2H), 1.17(m, 1H), 1.46(t, 3H), 3.73(m, 2H), 4.46(q, 2H), 6.93(t, 1H), 7.56(dt, 1H), 8.28(d, 1H), 8.86(br, 1H), 9.09(d, 1H)

Elementary analysis: C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>

		C%	H%	N%
10	Calcd.	65.58	5.50	13.50
	Found	65.56	5.37	13.31

3-Cyano-2-cyclopropylmethylamino-1-(3-phenylpropoxycarbonyl)-4H-quinolizin-4-one (S-28)

Melting point: 92-94°C

IR (KBr): 2200, 1660, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 0.38(m, 2H), 0.65(m, 2H), 1.15(m, 1H), 2.16(m, 2H), 2.78(t, 2H), 3.73(m, 2H), 4.40(t, 2H), 6.95(t, 1H), 7.18-7.36(m, 5H), 7.53(dt, 1H), 8.25(d, 1H), 8.90(br, 1H), 9.09(d, 1H)

Elementary analysis: C<sub>24</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>

		C%	H%	N%
25	Calcd.	71.80	5.77	10.47
	Found	71.77	5.77	10.55

3-Cyano-1-ethoxycarbonyl-2-(2-piperidinoethylamino)-4H-quinolizin-4-one (S-29)

Melting point: 119-120°C

IR (KBr): 2210, 1670, 1625 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.42(t, 3H), 1.62(br, 6H), 2.47(br, 4H), 2.62(br, 2H), 3.95(br, 2H), 4.47(q, 2H), 6.89(t, 1H), 7.49(dt, 1H), 8.15(d, 1H), 8.65(br, 1H), 9.04(d, 1H)

Elementary analysis: C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>

		C%	H%	N%
35	Calcd.	65.20	6.57	15.21
	Found	65.28	6.80	15.64

3-Cyano-1-(3-phenylpropoxycarbonyl)-2-(2-piperidinoethylamino)-4H-quinolizin-4-one (S-30)

Melting point: 110-111°C

IR (KBr): 2210, 1705, 1660, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.48(br, 2H), 1.60(br, 4H), 2.13(m, 2H), 2.45(br, 4H), 2.59(br, 2H), 2.77(t, 2H), 3.92(br, 2H), 4.43(t, 2H), 6.89(t, 1H), 7.17-7.35(m, 5H), 7.49(dt, 1H), 8.12(d, 1H), 8.72(br, 1H), 9.04(d, 1H)

Elementary analysis: C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O<sub>3</sub>

		C%	H%	N%
50	Calcd.	70.72	6.59	12.22
	Found	70.91	6.77	12.62

3-Cyano-1-ethoxycarbonyl-2-(4-tert-butoxycarbonylcyclohexylamino)-4H-quinolizin-4-one (S-31)

Melting point: 148-149°C

IR (KBr): 2200, 1720, 1675, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.00-2.21(m, 8H), 1.43(t, 3H), 1.44(brs, 9H), 3.73(t, 2H), 4.44(q, 2H), 6.93(t, 1H), 7.53(dt, 1H), 8.27(d, 1H), 8.97(br, 1H), 9.09(d, 1H)

Elementary analysis: C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>

	C%	H%	N%
Calcd.	65.59	6.65	9.56
Found	65.45	6.18	9.24

5

3-Cyano-1-ethoxycarbonyl-2-(2-tetrahydrofurylmethylamino)-4H-quinolizin-4-one (S-32)

Melting point: 87-89°C

IR (KBr): 2200, 1700, 1675, 1635 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.44(t, 3H), 1.60-1.77(m, 1H), 1.91-2.17(m, 3H), 3.73-4.22(m, 5H), 4.45(q, 2H), 6.92(t, 1H), 7.53(dt, 1H), 8.27(d, 1H), 8.97(br, 1H), 9.08(d, 1H)

Elementary analysis: C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>

10

	C%	H%	N%
Calcd.	63.33	5.61	12.31
Found	63.21	5.56	12.29

15

3-Cyano-1-ethoxycarbonyl-2-(2,2,6,6-tetramethylpiperidin-4-ylamino)-4H-quinolizin-4-one (S-33)

Melting point: 89-91°C

IR (KBr): 2210, 1670, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 0.87-1.27(m, 18H), 1.87(m, 2H), 4.14(q, 2H), 4.69(m, 1H), 6.63(t, 1H), 7.24(dt, 1H), 7.93(d, 1H), 8.45(d, 1H), 8.78(d, 1H)

Elementary analysis: C<sub>22</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>

20

	C%	H%	N%
Calcd.	66.65	7.12	14.13
Found	66.18	7.11	14.11

30

3-Cyano-1-ethoxycarbonyl-2-morpholinoamino-4H-quinolizin-4-one (S-34)

Melting point: 179-181°C

IR (KBr): 2210, 1710, 1675, 1635 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.46(t, 3H), 2.75(br, 2H), 3.07(br, 2H), 3.89(br, 4H), 4.46(q, 2H), 7.00(t, 1H), 7.60(dt, 1H), 8.27(br, 1H), 9.16(d, 1H), 9.35(br, 1H)

Elementary analysis: C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>

35

	C%	H%	N%
Calcd.	59.64	5.30	16.37
Found	59.94	5.34	15.78

45

3-Cyano-1-ethoxycarbonyl-2-(4-piperidinylmethylamino)-4H-quinolizin-4-one (S-35)

Melting point: 84-85°C

IR (KBr): 2210, 1660, 1630 cm<sup>-1</sup><sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.19-1.38(m, 2H), 1.46(t, 3H), 1.85(br, 4H), 2.68(t, 2H), 3.18(d, 2H), 3.75(t, 2H), 4.45(q, 2H), 6.95(t, 1H), 7.55(dt, 1H), 8.27(d, 1H), 9.05(br, 1H), 9.09(d, 1H)

Elementary analysis: C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>

50

	C%	H%	N%
Calcd.	64.39	6.26	15.81
Found	64.30	6.58	16.00

60

3-Cyano-1-ethoxycarbonyl-2-(1-indanylamino)-4H-quinolizin-4-one (S-36)

Melting point: 195-196°C

IR (KBr): 2200, 1670, 1650, 1630 cm<sup>-1</sup>

65

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.29(t, 3H), 2.13(m, 1H), 2.82-3.14(m, 3H), 4.34(q, 2H), 6.08(q, 1H), 6.95(t, 1H), 7.21-7.39(m, 4H), 7.54(dt, 1H), 8.26(d, 1H), 8.98(d, 1H), 9.12(d, 1H)

Elementary analysis: C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>

5

	C%	H%	N%
Calcd.	70.76	5.13	11.25
Found	70.37	5.15	10.95

10

3-Cyano-1-ethoxycarbonyl-2-(1,2-diethylpyrazolidin-4-ylamino)-4H-quinolizin-4-one (S-37)

Melting point: 80-82°C

IR (KBr): 2195, 1675, 1650, 1625 cm<sup>-1</sup>

15

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):

δ 1.12(t, 6H), 1.45(t, 3H), 2.73(m, 4H), 3.01(dd, 2H), 3.45(dd, 2H), 4.46(q, 2H), 5.19(m, 1H), 6.96(t, 1H), 7.56(dt, 1H), 8.26(d, 1H), 9.09(d, 1H), 9.20(d, 1H)

Elementary analysis: C<sub>20</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>

20

	C%	H%	N%
Calcd.	62.65	6.57	18.26
Found	62.59	6.64	17.82

25

## Test Example

Determination of Igs produced in in vitro culture

BALB/c mice were immunized intraperitoneally with 5 µg of DNP-As adsorbed on 4 mg aluminum hydroxide gel. Four weeks after the immunization, the spleens were excised from the mice and 5 x 10<sup>7</sup> spleen cells were transferred intravenously into the recipient mice which had been exposed to 600 rad of X-ray irradiation. Immediately after cell transfer, the recipients were then immunized intraperitoneally with 5 µg of DNP-As adsorbed on 4 mg aluminum hydroxide gel to induce adoptive secondary immune response. Further 4 weeks after the immunization of recipients, the spleens were excised from them and the spleen cell suspensions containing 5 x 10<sup>6</sup> cells/ml were cultured with or without a compound to be tested in 96-well micro-titer plates at 37°C for 4 days. IgE and IgG secreted into the culture supernatant was each determined correspondingly by ELISA and the inhibitory effect was calculated according to the following equation.

40

45

EMI ID=43/1 HE=35 WI=140 TI=MAT

50

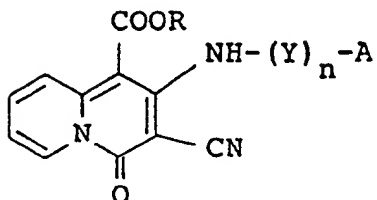
The results obtained were shown below:

Comp. No.	Concentration (µg/ml)	Inhibition % of IgE	Inhibition % of IgG
S- 1	20	60	13
S- 6	20	68	16
S- 14	10	72	1
S- 15	10	73	3
S- 16	20	68	7
S- 17	10	68	12

65

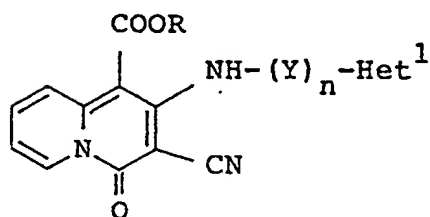
## Claims

1. A 4H-quinolizin-4-one compound of the formula:



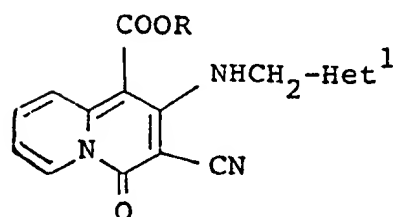
where R is an alkyl group or a phenylalkyl group; Y is an alkylene group, n is zero or 1, A is a substituted or unsubstituted 5 or 6 membered aromatic heterocyclic group, a substituted or unsubstituted 3 to 7 membered cycloalkyl group, or a substituted or unsubstituted 5 to 7 membered saturated heterocyclic group; or a pharmaceutically acceptable salt thereof.

2. A 4H-quinolizin-4-one compound of the formula:



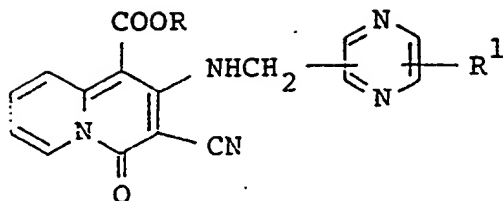
where R is an alkyl group or a phenylalkyl group, Y is an alkylene group, n is zero or one, Het¹ is a substituted or unsubstituted 5 or 6 membered aromatic heterocyclic group; or a pharmaceutically acceptable salt thereof.

3. A 4H-quinolizin-4-one compound of the formula:



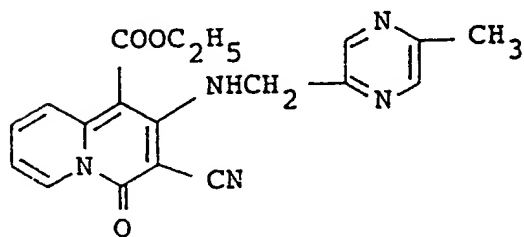
where R is an alkyl group or phenylalkyl group, Het¹ is a substituted or unsubstituted 5 or 6 membered aromatic heterocyclic group, or a pharmaceutically acceptable salt thereof.

4. A 4H-quinolizin-4-one compound of the formula:



10 where R is an alkyl group or phenylalkyl group, R<sup>1</sup> is a hydrogen atom or an alkyl group; or a pharmaceutically acceptable salt thereof.

5. A 4H-quinolizin-4-one compound of the formula:



; or a pharmaceutically acceptable salt thereof.

6. The use of a 4H-quinolizin-4-one compound as claimed in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of allergic bronchial asthma, allergic rhinitis, atopic dermatitis or hypersensitiveness.

7. A pharmaceutical composition comprising a 4H-quinolizin-4-one compound as claimed in any of claims 1 to 5 or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition for the treatment of allergic bronchial asthma, allergic rhinitis, atopic dermatitis or hypersensitiveness associated with immunoglobulin E in a mammal, which composition contains an effective dosage from about 0.1 mg to 10 mg per kg by oral administration or from about 0.2 mg to 5 mg per kg by parenteral administration per day of an immunoglobulin E-formation-inhibiting 4H-quinolizin-4-one compound as claimed in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof.

9. Any of the 4H-quinolizin-4-one compounds prepared in Examples 1 to 6.



(12)

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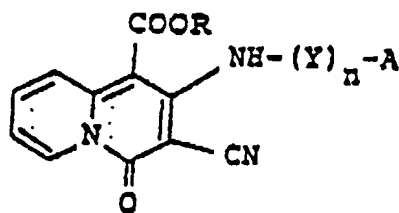
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(54) 4H-quinolizin-4-one compounds and pharmaceutical compositions containing them.

(57) 4H-Quinolizin-4-one compounds of the formula:



EP 0 317 295 A3

where R is an alkyl or phenylalkyl group; Y is an alkylene, n is zero or 1, A is an aromatic heterocyclic group, a cycloalkyl group, or a heterocyclic group; exhibit a selective inhibitory activity against IgE-antibody formation, and have utility for treatment of diseases associated with IgE formation in mammals, such as allergic bronchial asthma, allergic rhinitis, atopic dermatitis and hypersensitivity. The invention also provides pharmaceutical compositions containing such compounds.



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 157 346 (FUJISAWA) * Claims 1,12 * ----	1,7	C 07 D 455/02 A 61 K 31/44 A 61 K 31/495
P,A	EP-A-0 277 755 (KISSEI) * Claims 1,10 * -----	1,7	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 455/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 27-09-1990	Examiner ALFARO I.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			